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Dkt. 2793/65166/JPW/CMR

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Christos J. Petropoulos, et al.

Serial No.: 09/874,475

Filed : June 4, 2001

For : COMPOSITIONS AND METHODS FOR EVALUATING VIRAL
RECEPTOR/CO-RECEPTOR USAGE AND INHIBITORS OF
VIRUS ENTRY USING RECOMBINANT VIRUS ASSAYS1185 Avenue of the Americas
New York, New York 10036
September 4, 2001Assistant Commissioner for Patents
Washington, D.C. 20231

ATTN: Box Missing Parts

Sir:

**PRELIMINARY AMENDMENT IN RESPONSE TO JULY 2, 2001 NOTICE
TO FILE MISSING PARTS OF APPLICATION-FILING DATE GRANTED**

This Amendment is submitted in response to the July 2, 2001 Notice to File Missing Parts of Application-Filing Date Granted issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to this July 2, 2001 Notice is due September 2, 2001. However, since September 2, 2001 falls on a Sunday, the next succeeding day which is not a Saturday, Sunday or Federal Holiday, i.e. Tuesday, September 4, 2001, shall be considered timely under 37 CFR §1.7. Accordingly, this Amendment is being timely filed.

Applicant: CMSGS J. Petropoulos
Serial No.: 09/874,475
Filed: June 4, 2001
Page 2



Please amend the subject application as follows:

In the Specification

Please amend the specification by deleting the reference to Figure 10, Figure 11, Figure 12 and Figure 13 on page 11, lines 6-12.

Please also amend the specification by deleting the paragraph on page 59, lines 7-20 and inserting the following paragraph:

In one embodiment, drug resistance mutations were introduced into well-characterized X4 tropic (NL4-3) and R5 tropic (JRCSF) viruses. T20 susceptibility was measured using the virus entry assay (**Figure 7**). The fold change (FC) in T-20 susceptibility for each virus was determined by dividing the IC50 of the test virus by the IC50 of the HXB2 strain of HIV- 1. T-20 sensitivity of similar mutant viruses has been reported in the scientific literature (Rimsky et al.,). In this embodiment, viruses with one mutation within the GIV motif of gp41 (DIV, GIM, SIV) were less susceptible to T20 than the wildtype virus (GIV) (**Table 6**). Viruses with two mutations within the GIV motif (DIM, SIM, DTV) were less susceptible to T20 than viruses with one, or no mutations in the GIV motif (**Table 6**).

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Please amend the specification by deleting the paragraph on page 59, lines 22-32 to page 60, lines 1-5, and inserting the following paragraph:

In another embodiment, mutations that may confer reduced (or increased) susceptibility to the entry inhibitor are identified by sequencing the envelope genes of the sensitive and resistant viruses. The deduced amino acid sequences of the sensitive and resistant viruses are compared to identify candidate drug resistance mutations. The ability of a specific mutation to confer altered drug susceptibility is confirmed or disproved by introducing the mutation into a drug sensitive virus and measuring the susceptibility of the mutant virus in the virus entry assay. In the example represented here, a short stretch of amino acid sequences within the first heptad repeat (HR-1) of the HIV-1 gp41 transmembrane envelope protein is aligned for viruses exhibiting different T-20 susceptibilities (**Table 6**). Highlighted amino acids represent mutations known to confer reduced susceptibility to T-20.

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Filed: June 4, 2001
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REMARKS

The Notice to File Missing Parts of Application indicates that the oath or declaration is unsigned. Applicants attach hereto a copy of the Notice as **Exhibit A**. In response, applicants submit as **Exhibit B** hereto a signed Declaration and Power of Attorney pursuant to 37 C.F.R. §1.53(f). In compliance with 37 C.F.R. §1.63, the Declaration refers to the application's above-identified serial number and filing date.

Drawings in Compliance with 37 C.F.R. §1.84

The July 2, 2001 Notice also indicates that the drawing sheets do not have the appropriate margins and contain excessive text. The July 2, 2001 Notice stated suitable descriptive legends may be used, or may be required by the Examiner where necessary for understanding of the drawings but should contain few words as possible.

Applicants elect to provide the required amendment and/or correction to the drawing Figures 1-9 by way of Preliminary Amendment submitted with a Petition for an extension of time under the provisions of 37 C.F.R. 1.136(a) as the July 2, 2001 Notice indicates as an option.

Sequence Listing in Compliance with 37 C.F.R. §1.821-1.825

The July 2, 2001 Notice indicates that the subject application fails to comply with the requirements of 37 C.F.R. §1.821-1.825 for sequence listings.

In response to the July 2, 2001 Notice, applicants submit a paper copy and computer readable copy of the nucleotide and/or amino acid sequences disclosed in the application in order to fulfill the requirements of 37 C.F.R. §1.821 and §1.825 in connection

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with this application. Applicants submit herewith six (6) pages of Sequence Listing in compliance with the requirements of §1.821 and §1.825 attached hereto as **Exhibit C**.

Applicants also submit herewith a formatted Sequence Listing in a computer readable form which complies with the requirements of 37 C.F.R. §1.824. In addition, applicants submit a Statement in Accordance with 37 C.F.R. §1.821(f), attached hereto as **Exhibit D**, certifying that the computer readable form containing the nucleic acid and/or amino acid sequences as required by 37 C.F.R. §1.821(e) contains the same information which is submitted as "Sequence Listing".

Amendment to the Specification

The July 2, 2001 Notice of Incomplete Reply stated that Figures 10-13 described in the subject application were missing.

In response and solely to advance prosecution, applicants have amended the specification on pages 11, lines 6-12 to delete the reference to Figures 10-13, and on page 59, lines 7-20 and page 60, lines 1-5, to delete the reference to "Figure 11" and replace it with "Table 6". **Exhibit E** attached hereto sets forth the amended paragraphs on page 59, lines 7-20, and page 59, lines 22-32 to page 60, lines 1-5, which have been marked up to show the changes relative to the previous versions thereof.

Support for the amendments to the specification replacing the reference to "Figure 11" with "Table 6" can be found *inter alia*, on line 1 of Table 6, as line 1 of Table 6 refers to "T20 Resistance Mutations", as does the previous reference to Figure 11 on page 11 of the specification.

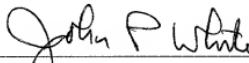
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Applicants submit that these amendments are fully supported by the specification and do not raise any issue of new matter. Therefore, applicants respectfully request that these amendments be entered.

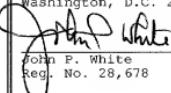
No fee, other than the enclosed fee of SIXTY-FIVE DOLLARS (\$65.00) is deemed necessary in connection with the filing of this Amendment. If any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125

Respectfully submitted,



John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Assistant Commissioner for Patents,
Washington, D.C. 20231.

 9/4/01

John P. White	Date
Reg. No. 28,678	

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Figure 10. Inhibition by Co-Receptor Antagonists

Figure 11. T20 Resistance Mutations

Figure 12. Identifying Entry Inhibitor Resistance Mutations

Figure 13. Fusion Inhibitor Peptides

In one embodiment, drug resistance mutations were introduced into well-characterized X4 tropic (NL4-3) and R5 tropic (JRCSF) viruses. T20 susceptibility was measured using the virus entry assay (**Figure 7**). The fold change (FC) in T-20 susceptibility for each virus was determined by dividing the IC50 of the test virus by the IC50 of the HXB2 strain of HIV-1. T-20 sensitivity of similar mutant viruses has been reported in the scientific literature (Rimsky et al.,). In this embodiment, viruses with one mutation within the GIV motif of gp41 (DIV, GIM, SIV) were less susceptible to T20 than the wildtype virus (GIV) (**Figure 11 Table 6**). Viruses with two mutations within the GIV motif (DIM, SIM, DTV) were less susceptible to T20 than viruses with one, or no mutations in the GIV motif (**Figure 11 Table 6**).

In another embodiment, mutations that may confer reduced (or increased) susceptibility to the entry inhibitor are identified by sequencing the envelope genes of the sensitive and resistant viruses. The deduced amino acid sequences of the sensitive and resistant viruses are compared to identify candidate drug resistance mutations. The ability of a specific mutation to confer altered drug susceptibility is confirmed or disproved by introducing the mutation into a drug sensitive virus and measuring the susceptibility of the mutant virus in the virus entry assay. In the example represented here, a short stretch of amino acid sequences within the first heptad repeat (HR-1) of the HIV-1 gp41 transmembrane envelope protein is aligned for viruses exhibiting different T-20 susceptibilities (**Figure 11 Table 6**). Highlighted amino acids represent mutations known to confer reduced susceptibility to T-20.



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Dkt. 2793/65166/JPW/AJM/DRM

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Christos J. Petropoulos et al.

Serial No.: 09/874,475

Filed : June 4, 2001

For : COMPOSITIONS AND METHODS FOR EVALUATING VIRAL
RECEPTOR/CO-RECEPTOR USAGE AND INHIBITORS OF
VIRUS ENTRY USING RECOMBINANT VIRUS ASSAYS

1185 Avenue of the Americas
New York, New York 10036
February 4, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

ATTN: Box Missing Parts

Sir:

**SECOND PRELIMINARY AMENDMENT IN RESPONSE TO
JULY 2, 2001 NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL
APPLICATION AND PETITION FOR A FIVE-MONTH EXTENSION OF TIME**

This Second Preliminary Amendment is submitted in response to a July 2, 2001 Notice to File Missing Parts of Nonprovisional Application issued by the United States Patent and Trademark Office in connection with the above-identified application. A response to the July 2, 2001 Notice was originally due on September 2, 2001. Applicants hereby petition for a five-month extension of time from September 2, 2001 to February 2, 2002. The required fee for a five-month extension of time is \$980.00 and a check in this amount is enclosed. However, since February 2, 2002 falls on a Saturday, a response filed on the next business day, i.e. Monday, February 4, 2002, shall be considered timely. Accordingly, this Amendment is being timely filed.

Applicants: Christos J. Petropoulos et al.
Serial No.: 09/874,475
Filed: June 4, 2001
Page 2

Please amend the subject application as follows:

In the Figures

Please cancel Figures 1-9 and insert new Figures 1-9.

REMARKS

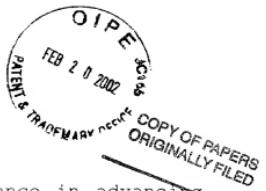
The July 2, 2001 Notice requires applicants to submit: (a) a signed oath or declaration and required fee; (b) a Sequence Listing in compliance with 37 C.F.R. §1.821-1.825; and corrected Substitute Figures.

On September 4, 2001, applicants submitted a Preliminary Amendment forwarding a signed Declaration and Power of Attorney, a paper copy and computer readable copy of the nucleotide and/or amino acid sequences disclosed in the application, and a Statement in Accordance with 37 C.F.R. §1.821(f). Applicants also amended the subject application to delete Figures 10-13 and any references thereto in the specification.

This Second Preliminary Amendment is being submitted in order to replace originally submitted Figures 1-9 with new Figures 1-9 corrected to address the informalities as set forth in the Notice. Accordingly, applicants annex hereto as **Exhibit A** a copy of the July 2, 2001 Notice, and annex hereto as **Exhibit B** corrected Figures 1-9. As required by the Notice, applicants have also amended the subject application hereinabove to delete originally filed Figures 1-9 and insert new Figures 1-9 corresponding thereto, respectively.

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If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone at the number provided below.

No fee, other than the enclosed \$980.00 fee for the five-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Alan J. Morrison
Registration No. 37,399
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

Assistant Commissioner for Patents,
Washington, D.C. 20231.

Alan J. Morrison
Reg. No. 37,399

+ 2/4/02

Date

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